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HISTOPLASMOSIS IN THE DISTRICT OF COLUMBIA, MARYLAND AND VIRGINIA

Chester W. Emmons, Ph.D.,* Charlotte C. Campbell, B.S.†

There is increasing evidence that histoplasmosis is more highly endemic in the eastern United States than was heretofore supposed. This is particularly true of the states of Maryland and Virginia and possibly southeastern Pennsylvania. *Histoplasma capsulatum* has been isolated recently from 11 residents of these 3 states, and more importantly from soils on 22 premises to which some of these persons were directly exposed. There were 35 additional persons with significant serologic titers to Histoplasma antigens on whom the more definitive cultural studies could not be carried out. (See Table V). Each of the latter patients had resided in the Maryland-Virginia area for at least 2 years prior to his illness, and the clinical symptoms of each were consistent with those seen in culturally verified cases of histoplasmosis.

The data to be reported herein were compiled independently by the authors in the study of sporadic and individual cases observed in the civilian and military hospitals of the District of Columbia and other cities in this region. We are indebted to the many clinicians whose cooperation and interest made these collective studies possible, for it is the latter that have led to the increased cognizance of histoplasmosis in this eastern region that heretofore was largely regarded as non-endemic.

MATERIALS AND METHODS

The procedures used in isolating *Histoplasma capsulatum* from soils[1] and clinical specimens[2], as well as those for the complement fixation (CF)[3, 4] and collodion agglutination (CA)[5] serologic tests are each described in earlier reports.

RESULTS

Soil Studies: In a search for saprophytic sources of Histoplasma and other pathogenic fungi, 2586 specimens of soil and organic debris have been ex-

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amined. Results of some of these studies were reported in 1954[6]. These studies first established that *Histoplasma capsulatum*[1] and *Cryptococcus neoformans*[7, 8] are frequently present as saprophytes in certain types of organic debris or enriched soil and have confirmed the observations of others[9] that Histoplasma is most often isolated from the soil and litter in and around chicken houses[6].

Nearly 80 per cent of the soil specimens examined were collected within a 75 mile radius of Washington, D. C., the remainder coming from Wisconsin, New York, Georgia, Panama, South Africa, Japan, and Egypt. Studies were begun in Northern Virginia where the occurrence of 4 fatal cases of histoplasmosis had aroused local public interest in the disease[10]. Subsequent field studies revealed that in this area 83 per cent of the general population reacted to the histoplasmin intradermal test and 41 per cent had pulmonary calcification[11]. Extension of the field studies to animal hosts yielded 309 isolations of Histoplasma from 4,664 animals collected; the infected animals represented 8 species[12]. The most productive techniques used indicated that half the dogs in the area under study had actual but inapparent histoplasmosis[2].

In the soil studies made in Virginia and only partially reported previously [6] 728 soil samples were taken from 35 premises. Histoplasma was isolated by mouse inoculation from 86 of the 728 specimens (11.8 per cent), and from 13 of the 35 premises (35 per cent). These percentages are of little or no significance since the specimens were not taken from premises distributed at random over the rural area under study. Five of the premises sampled were associated with human infections, and infected animals had been taken from all but 4 of the remaining premises. Furthermore, multiple and repeated collections were made from some of the premises which for one reason or another were of special interest. For example, 103 samples (4 collections) were taken from the premises where Histoplasma was first isolated[1] and 10 of these were positive. Histoplasma was isolated from 33 of 201 samples (10 collections) on a farm where many isolations were made from the dirt floor of a meat house[6]. This unusual site stimulated our interest and recurrent sampling. Data concerning the premises from which Histoplasma was isolated are given in Table I.

Obviously, political boundaries do not determine the saprophytic distribution of Histoplasma, and it has been apparent from scattered observations over a period of several years that Histoplasma is present in soil in appropriate sites in Maryland and may be as frequent there as in Virginia. Some of the earlier evidence comes from the occurrence of human cases of proved histoplasmosis in Maryland. In September, 1952, Histoplasma was isolated from 5 of 53 soil samples taken from a farm in Frederick County, Maryland. Benign histoplasmosis was suspected in some of the residents of this farm, but the diagnosis could not be substantiated.

TABLE I

Isolation of H. capsulatum from Soils from 21 Premises in Maryland and Virginia and One in Southeastern Pennsylvania

No.	Nearest Town	County	State	Comment
1	Lucketts	Loudoun	Virginia	*H. capsulatum* also isolated from animals on premises
2	Lucketts	Loudoun	Virginia	*H. capsulatum* also isolated from animals on premises
3	Ashburn	Loudoun	Virginia	*H. capsulatum* also isolated from animals on premises
4	Ashburn	Loudoun	Virginia	*H. capsulatum* also isolated from animals on premises
5	Ashburn	Loudoun	Virginia	*H. capsulatum* also isolated from animals on premises
6	Ashburn	Loudoun	Virginia	*H. capsulatum* also isolated from animals on premises
7	Ashburn	Loudoun	Virginia	*H. capsulatum* also isolated from animals on premises
8	Ashburn	Loudoun	Virginia	*H. capculatum* also isolated from animals on premises
9	Sterling	Loudoun	Virginia	*H. capsulatum* also isolated from animals on premises
10	Sterling	Loudoun	Virginia	*H. capsulatum* also isolated from animals on premises
11	Warrenton	Fauquier	Virginia	See Case 3, Table II
12	Midland	Fauquier	Virginia	See Case 6, Table III
13	Centreville	Fairfax	Virginia	See Case 7, Table III
14	Leonardtown	St. Mary's	Maryland	See Case 5, Table II
15	Urbana	Frederick	Maryland	No proved human case, serology negative
16	Clarksburg	Montgomery	Maryland	Proved or clinically typical case, serology inadequate
17	Gaithersburg	Montgomery	Maryland	Proved or clinically typical case, serology inadequate
18	Comus	Montgomery	Maryland	Proved or clinically typical case, serology inadequate
19	Gaithersburg	Montgomery	Maryland	Proved or clinically typical case, serology inadequate
20	Wheaton	Montgomery	Maryland	See Cases 1 & 2, Table II, 8, 9 and 10, Table III
21	Rockville	Montgomery	Maryland	See Case 11, Table III
22	Kennett Square	Chester	Pennsylvania	See Case 4, Table II

Examination of soil samples from Maryland was begun in 1948. Studies have not been carried on as extensively or as consistently as in Virginia, but Histoplasma has been isolated from 74 of the 639 specimens (11.5 per cent). Positive specimens have come from 8 of 23 premises. Six of these 8 premises are in Montgomery County. Only negative specimens were collected from 8

TABLE II

Serologic Reactions in Local Cases in which H. capsulatum was Isolated from the Patient and from Soil to which He was Exposed 10–21 Days Before Onset of Illness

Case	CF titer		CA titer	Hospital	Comment
	WYP*	H†	H†		
1	64	—‡	64+	Mt. Alto	Soil samples collected from floor of old chicken house on farm within 5 miles of the city limits of the District of Columbia.
2	64	—	64+	Not Hospitalized	
3	512	—	64	Mt. Alto	Resident of D. C. Soil sample collected from old chicken house near Warrenton, Virginia from which patient flushed rabbit while hunting.
4	512	64	32	George Washington	Soil collected from patient's back yard in Chester Co., Penna. Recent site of old chicken house.
5	—	—	64	D. C. General	Soil collected from around old chicken house on farm near Leonardtown Md. where patient frequently visited.

* Whole yeast phase antigen of *H. capsulatum*.

† Histoplasmin, derived from filamentous growth phase of organism.

‡ A dash indicates a negative test.

additional premises in Montgomery County. Other sites studied are in Carroll, St. Mary's, Anne Arundel and Frederick Counties.

Examinations of soil in Maryland have been stimulated mainly (and to a greater extent than in Virginia) by human case association. An environmental source of human infection was suspected on 23 of the 27 premises sampled in Maryland. From 1 to 3 premises were sampled in connection with each of the proved or suspected cases of histoplasmosis and each of the 8 Maryland premises from which Histoplasma was isolated may have been the source of infection in an individual or family outbreak.

On 5 of the Maryland premises, Histoplasma was isolated only from chicken houses or chicken house litter; on one it was isolated only from the site of a chicken house removed 3 years before[6]; and on one it was isolated from several areas to which chickens had free access. In one case, which is under more detailed study, there was no apparent association with chickens. On one farm near Leonardtown, Maryland, Histoplasma was isolated from 42 of 142 specimens[6]. Although soil specimens were taken from around each of several barns and outbuildings on the farm, Histoplasma was

TABLE III

Serologic Reactions in Local Cases in which H. capsulatum was Isolated from Soil with which Patients had Contact Before Onset of Illness, but not from the Patient

Case	CF Titer		CA titer	Hospital	Comment
	WYP*	H†	H†		
6	256	—‡	—	Children's	Soil collected from around chicken house at patient's home near Midland, Va.
7	512	—	64+	Georgetown	Soil collected from around chicken coop near Centreville, Va. where patient resided.
8	256	256	64+	Not hospitalized	See comment cases 1 and 2, Table II
9	64	—	64+	Not hospitalized	See comment cases 1 and 2, Table II
10	64	—	64+	Not hospitalized	See comment cases 1 and 2, Table II, and [16].
11	512	—	64+	Not hospitalized	Soil collected from chicken house on farm near Rockville, Md. where patient was employed.

*, † and ‡, see Footnotes Table II.

isolated only from inside or adjacent to a small chicken house. Repeated sampling at various times of the year have shown Histoplasma to be persistently present at this site. This was the presumptive source of infection of a patient with severe generalized (but not fatal) histoplasmosis. The patient lived in Washington, D. C. where we tried unsuccessfully to isolate the fungus, but he had frequently visited the farm near Leonardtown. It is interesting that Leonardtown is located in the tidewater area of Maryland.

Three sites within the District of Columbia have been examined. All were the residences of patients with histoplasmosis who could have been infected in the District of Columbia or could have had other unrecognized exposures. Histoplasma was not isolated from any of the 47 specimens collected on these premises.

Serologic data: Cultural and other available pertinent data in 52 serologically positive cases of histoplasmosis are summarized in Tables II, III, IV and V. The positive serologic findings were supported by isolation of *H. capsulatum* from the patient and from the local soil source to which he was recently exposed in the 5 cases in Table II, from nearby soil sources directly associated with the 6 cases in Table III, and from each of the 6 patients in Table IV. Although there was no opportunity to pursue cultural studies in a majority of the 35 serologically presumptive cases in Table V,

TABLE IV

Serologic Reactions in Local Cases in which H. capsulatum was Isolated from the Patient but not from Associated Soil Sources in Nature (Attempts Were not Made in Six of the Seven Cases)

Case	CF titer		CA titer	Hospital	Comment
	WYP*	H†	H†		
12	2048	128	—‡	University, Baltimore	Fatal case in 2 yr. old girl Resident of Winchester, Va. Had travelled only to adjacent counties in W. Va.
13	32	—	—	Suburban, Bethesda	Resident Bethesda, Md.
14	64	—	64+	Walter Reed, D. C.	Medical Officer, USA. Resident of Montgomery Co., Md. for past 6 years
15	—	1024	64+	Walter Reed, D. C.	Army dependent. Resident Alexandria, Va. past 2 years
16	128	32	—	Walter Reed, D. C.	Army dependent. No travel beyond North Carolina. Resident nearby Va. for past 3 years
17	128	—	64	Naval Med. Center	Medical Officer, USN. Resident Montgomery Co., Md. for past 3 yrs.

*, † and ‡, see Footnotes Table II.

there was a history of exposure similar to that in the cultura ly verified cases in many of these patients, particularly patients 18 through 30.

DISCUSSION

The isolation of *H. capsulatum* from soils in any particular geographic area is perhaps the most conclusive evidence that infection in man and animal can be expected to occur in that region[6]. While there has been no systematic soil sampling survey, Histoplasma has been isolated from soil samples taken from 21 different sites in the states of Maryland and Virginia and one in bordering southeastern Pennsylvania (Table I). It is of interest to note that this total of 22 premises comprises twice as many as were recorded in the epidemics described by Grayston and Furcolow[12], although these epidemics, with one exception in New York, occurred in the central United States, which was already recognized as an endemic area. In retrospect, therefore, it is quite possible that there is more than historical significance to the fact that the first isolation of *H. capsulatum* from any natural source was in soil collected in nearby northern Virginia[1].

TABLE V

Data in 35 Additional Serologically Presumptive Cases in the Local Area

Case	CF ttier		CA titer	Hospital	Comment
	WYP*	H†	H†		
18	64	128	64	University, Baltimore	Patients were brothers who removed manure from a barn near Taneytown, Md., 1–2 weeks prior to onset of infection. This outbreak mentioned but not described by Grayston and Furcolow [12].
19	8	—‡	64		
20	AC§	AC	32		
21	64	16	64+	Children's, D. C.	Resident Alexandria, Va. Patient had recently played in chicken houses in Little Washington and Vienna, Va.
22	64	—	64+	Garfield, D. C.	Resident Vienna Woods, Va. Gardens extensively, using chicken compost from farms in Va. and Md.
23	512	8	16	Arlington, Va.	Resident Fairfax, Va. Cleaned chicken coop on an aunt's farm near Leesburg, Va., two weeks prior to onset of illness.
24	64	—	—	Mt. Alto, D. C.	Resident D. C. Visits farms in Montgomery Co., Md. frequently.
25	64	—	64+	Fort Detrick, Md.	Patients cleaned old chicken house on farm near Frederick, Md. two weeks before onset.
26	128	—	64+		
27	128	—	64	Veterans Administration Hospital, Martinsburg, West Va.	Patient resides on farm near this town.
28	32	—	16	Veterans Administration Hospital, Martinsburg, West Va.	Patient resides on farm near this town.
29	16	64	—	Veterans Administration Hospital, Martinsburg, West Va.	Patient resides on farm near this town.
30	128	—	32	Clinical Center, NIH	Patient resides on farm near Potomac, Md.
31-39	32 to 128	—	16 to 64+	Bolling Air Force Base and Ft. Belvoir	Patients were all service personnel or dependents thereof who had resided for at least the past two years in local areas

TABLE V—*Continued*

Case	CF titer		CA titer	Hospital	Comment
	WYF	H	H		
40	16	—	—	Not hospitalized	Resident Silver Spring, Md. with coin lesion. Histoplasmin skin test positive, PPD negative
41	128	16	64+	Emergency, D. C.	Resident D. C. No further information
42	256	—	64	D. C. General	No additional information
43	128	—	64	D. C. General	No additional information
44	64	—	—	D. C. General	No additional information
45	32	—	16	D. C. General	No additional information
46	—	16	—	Children's, D. C.	No additional information
47	256	—	—	Garfield, D. C.	No additional information
48	16	—	—	Garfield, D. C.	No additional information
49	8	—	64	George Washington	No additional information
50	32	—	—	Georgetown	No additional information
51	32	—	—	Glendale Sanatorium	No additional information
52	16	—	—	Glendale Sanatorium	No additional information

*, † and ‡, see Footnotes Table II.
§ A. C. indicates anticomplementary.

There is also clinical evidence that histoplasmosis in this eastern area may be frequently overlooked or misdiagnosed. A fatal case of the infection (the fourth to be reported in the United States) was described at Children's Hospital of D. C. in 1939[14]. By 1946 there were at least 4 additional fatal cases in residents of northern Virginia[10]. However, at that time the infection was still regarded as rare and invariably fatal, and, as in the central United States where the more extensive skin test surveys strongly suggested the high prevalence of a benign phase of the disease, the primary, pulmonary infection was not observed until much later. In 1952, there was a culturally verified outbreak of the acute infection in 4 members of a family residing in Montgomery County, Md. (Cases 1 and 2, Table II, and cases 8 and 9, Table III)[15]. The probable source of infection was exposure to chicken compost collected from a small coop on a farm located within 5 miles of the city limits of the District of Columbia[16]. Since then, the primary pulmonary infection has been observed in 46 of the 48 additional culturally verified or serologically presumptive cases reported herein. There is good evidence that even in the 1 fatal case (case 12, Table IV) the infection was acquired less than 3 months prior to death.

A review of these data leaves little reason for continuing to link the acquisition of histoplasmosis necessarily with residence, recent travel or

military service in the central United States. The primary infection was observed in veterans or dependents thereof whose infection arose only after exposure to foci in the Washington area (Cases 1, 2, and 3, Table II), and in lifelong residents of nearby eastern states who for various reasons were patients in local civilian hospitals (Case 4, Table II). Histoplasmosis, moreover, was seen in persons who were known to have been long-time residents of the central United States, but whose acute infections did not occur until after transfer to the eastern area. Cases 25 and 26, Table V, were lifelong residents in the Mississippi River Valley, and had always been in good health prior to onset of their acute pneumonitic infections. These infections began 2 weeks after the patients cleaned an old chicken house on a recently purchased farm near Frederick, Md. Although cultural studies were not carried out on these patients or on the soil to which they were exposed, the clinical symptoms, roentgenologic findings and positive serologic reactions were consistent with those in many culturally verified cases of primary, pulmonary histoplasmosis. For this reason, the culturally verified and serologically presumptive primary cases in military personnel in Tables IV and V were also included as infections that might have been acquired in the local area, as each had been a resident thereof for the past 2 to 6 years.

There were only two instances in which *H. capsulatum* was isolated from soils that were not contaminated with chicken excreta. Although the reason for the affinity of *H. capsulatum* for this particular type of medium[1, 6, 9] has not yet been adequately determined, there is no longer any doubt that it exists. The diagnosis of histoplasmosis must, therefore, be increasingly considered not only in rural residents but in the heterogeneous populations of surburban housing developments where gardening is a common pursuit and chicken fertilizer is readily accessible[16]. Nor should histoplasmosis be overlooked in the more urban citizen who gardens as a hobby[17] or visits friends or relatives in the country (Case 5, Table II, and Cases 21, and 23, Table V).

The presumptive serologic diagnosis of histoplasmosis is, of course, in some cases highly debatable. It is known that the mycotic antigens cross react to a marked degree, and that especially in patients who have lived in areas known to be endemic for blastomycosis and coccidioidomycosis as well as histoplasmosis, cross reaction can be especially troublesome[18]. On the other hand, the positive serologic reaction often provides the first supporting evidence that an infection is mycotic in origin, as was true in the majority of the culturally verified cases in this series of patients. Further, in histoplasmosis the positive serologic reaction is nearly always demonstrable during the early acute phase of illness when cultural studies, which under ordinary circumstances are seldom made for mycotic agents, are also most rewarding. The testing of serial serum specimens taken shortly after

onset and at weekly intervals thereafter often provides valuable diagnostic information, although too few cases have yet been followed from onset to associate serologic reaction patterns with prognostic evaluation in this extremely protean disease. A negative serologic reaction, unfortunately, does not exclude the possibility of infection, as the level of antibody varies with the type, degree, and duration of infection[18]. CF antibodies, even in sera from some of the milder culturally verified cases, may no longer be demonstrable in as little as 2 months after onset. The testing of early serial specimens is thus an important factor in the finding of the primary, pulmonary case, for it provides a rapid means of presumptively differentiating this infection from the clinically indistinguishable and supposedly more common pneumonitis of bacterial or viral etiology.

SUMMARY

H. capsulatum has been isolated from soils from 22 premises in the states of Maryland, Virginia and Pennsylvania. In many of the 52 culturally verified or serologically presumptive cases of histoplasmosis reported herein the patients were exposed directly to these soils. The slowly accumulating evidence of the high prevalence of this infection in this eastern area of the United States, not heretofore regarded as endemic, is outlined and discussed.

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ATHYREOTIC CRETINISM

Natividad Z. Pangan, M.D.*

Cretinism is a condition caused by a congenital deficiency of thyroid hormone. It may occur in endemic form with or without goiter, or in sporadic form. There are three types of the sporadic form: non-endemic goitrous, secondary (pituitary), and athyreotic. Since the prognosis for normal physical development depends on how early the condition is treated, and since the mental deterioration which has occurred before therapy is not reversible, early diagnosis of cretinism is of utmost importance. Although deficiency of thyroid hormone is present before birth, it is frequently not recognized unless suspected until the infant is about 9 months old when retardation, both physical and mental, is evident.

An athyreotic (sporadic) cretin is presented as an example of early diagnosis and treatment of the defect and the outcome after prolonged therapy.

CASE REPORT

This 2 months and 19 days old white female infant was admitted to Children's Hospital with the chief complaints of vomiting and constipation followed by diarrhea. She was the product of 9 months gestation. Her mother had mumps during the third month of pregnancy and had had one day of vaginal bleeding during the course of the disease. The infant was delivered by low forceps extraction after 3 hours of labor.

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The infant had been constipated since birth and required regular enemas. She vomited 2 to 3 times a day following meals. Her abdomen had always appeared distended and she frequently passed much flatus. Her mother had noticed a persistent circumoral cyanosis, a dry, coarse, mottled skin and a large tongue.

Family history revealed a healthy mother who was 28 years old and a father 26 years old. The infant had 2 brothers, 1 of whom had congenital heart disease. Both paternal and maternal grandmothers died of cancer and her paternal grandfather died of cancer and pulmonary tuberculosis.

At examination the baby's rectal temperature was 97.2 degrees, pulse rate 88 per minute, and respiratory rate 24 per minute. Her weight on admission was 11 pounds, 4 ounces. She was hypoactive and had a noticable pallor of her mucous membranes and nail beds. The anterior and posterior fontanelles were open. Her pupils were symmetrical but reacted very sluggishly to light. There was a bilateral internal strabismus. There was a questionable mid-systolic soft murmur at the apex which was not transmitted. Both lung fields were hyperresonant and contained a few coarse breath sounds. The abdomen was protuberant, hard, and tympanitic with diminished bowel sounds. There was a small reducible umbilical hernia.

Because of the history of vomiting, constipation and abdominal distention, the initial diagnostic impression was partial intestinal obstruction. X-ray of the abdomen with bar um enema revealed an intussusception which was reduced by the enema. Six days after the first barium enema another was done which demonstrated marked difficulty in passing barium from the splenic flexure to the transverse colon. The impression was of a sliding intussusception or possibly a duplication of the bowel.

Laboratory studies included: hemoglobin of 7.5 gm. per 100 ml., hematocrit of 21 per cent, leucocyte count of 11,600 per cu. mm. with 39 per cent segmented forms, 52 per cent lymphocytes, 6 per cent monocytes, 3 per cent eosinophils, and adequate platelet count. There was a moderate hypochromia with anisocytosis, and 1 cell with basophilic stippling. After 100 cu. mm. of whole blood was given the hemoglobin rose to 13.4 gm. per 100 ml. Repeated urinalyses were normal. Serum cholesterol was 148 mg. per 100 ml. Protein bound iodine on 2 occasions was 3 mcg. per 100 ml. Radio-active iodine uptake was less than 10 per cent. Fluoroscopy showed a full sized heart which was questionably enlarged. An electrocardiogram was interpreted as probably indicative of first degree atrio-ventricular block. Because the history and physical findings suggested cretinism which was substantiated by a low protein bound iodine determination and a low radio-active iodine uptake, the infant was given 15 mgm. of desiccated thyroid extract daily starting at the age of 3 months. She was discharged on the twelfth hospital day and was subsequently followed in the Endocrinology Clinic.

In less than 2 weeks following initiation of treatment she appeared much more active and possibly improved a bit in appearance although she had gained only 2 ounces in weight. After 3 months of therapy her hair had become soft and silky, and she had gained 6 pounds 9 ounces. During the sixth month of treatment she was found to fall in the seventy-fifth percentile for weight, whereas she had been in only the twenty-fifth percentile prior to therapy.

At age 10 months, a resection of the medial recti for the convergent strabismus was done. At age 1 year she still had a persistent external rotation of the right leg despite attempts at correction with night splints as suggested by the orthopedic department. X-ray examination of her hips, femoral epiphyses, and acetabular angles did not show any abnormality.

She was started on L-triiodo-thyronine at age 12 months. The dose was gradually increased to 75 mcg. per day but reduced to 50 mcg. per day when she was 15 months old.

At 16 months of age she weighed 29 pounds, was 32 inches tall, and had a 20 inch circumference of both head and chest. She was then in the ninety-seventh percentile (Boston Children's growth charts).

All the central incisors had erupted. She could say "mommy" and "daddy", held her own bottle, sat up indefinitely, pulled herself up to stand and played with her brothers. Her behavioral developmental age was equivalent to a 40 weeks level.

X-ray of her left wrist, evaluated according to the standards of Guenlich and Pyles, indicated bone maturation consistent with her chronological age or very slightly retarded.

DISCUSSION

The thyroid hormone insufficiency in the athyreotic type of sporadic cretinism may be due to either maldevelopment of the thyroid gland or to atrophic changes in the fetal gland brought about by an acute thyroiditis secondary to an infectious disease in the mother during pregnancy.

Although heredity is seldom considered a factor, Ainger and Kelly recently reported the unusual occurrence of athyreotic cretinism in 3 siblings whose father and mother were first cousins and whose family history was strongly suggestive of cretinism. Examination of their genealogic background revealed at least 12 additional closely related individuals who may have been similarly affected. In this family the athyreosis probably was due to a specific inherited defect in the gene.

The pathologic changes in the thyroid itself are quite variable. In some cases the thyroid is absent or so defective in development that remnants are difficult to find. The gland may appear inactive and atrophic microscopically. Changes in other organs may be similar to those found in myxedema. The bone marrow tends to be hypoplastic. Muscular tissue may show fatty infiltration. Sexual organs including gonads fail to develop properly and remain small. There appear to be no specific changes in the nervous system. Bronstein and Shadakharaffa described the brain of a 10 month old completely athyreotic infant: "The brain externally appeared to be normal and looked like that of a newborn infant. Microscopically, the cortical neurons showed very markedly vacuolated cytoplasm like that of an acute anoxia. The cerebellum was normal".

The symptomatology of athyreotic cretinism varies. In some cases the earliest complaints are vomiting, difficulty in feeding, inability to suck, extreme lethargy, and constipation. These may occur within a few days after birth and may be misdiagnosed as intracranial damage.

The typical cretin presents the appearance of a dwarf with infantile body proportions, and with marked physical, mental, and sexual retardation. The face is coarse and puffy, the tongue broad, large and thick, the voice hoarse,

the hair coarse and dry, and the skin pasty, cold, dry and sallow or possibly yellow due to carotenemia. The abdomen is protuberant and there is a persistent umbilical hernia. The hands are spade-like. The thick short neck is due to myxedematous deposits above the clavicles. The character of the voice and sensitivity to cold are attributable to the myxedematous change. The hypotonia of the musculature of the intestinal tract and the abdominal wall are responsible for constipation, abdominal distention and umbilical hernia.

The most available and reliable single test of use in diagnosis is the determination of the serum protein bound iodine since it represents the iodine of the circulating thyroid hormone. In the newborn the normal value is about 8.3 mcg. per 100 ml. It rises steadily to reach its peak during the first 2 weeks of life when it may be 21 mcg. per 100 ml., and then slowly drops to its near adult level of 4–8 mcg. per 100 ml. at 1 year of age. False high values may be obtained if the patient has had recent intravenous urography, iodine containing drugs, or even iodine on the skin. In the absence of such exposure a value of 3 mcg. per 100 ml. or less is diagnostic of hypothyroidism.

The determination of the serum cholesterol level is a simpler but less reliable test. It is increased in hypothyroidism but it should be remembered that in infants it is normally high and in young children it may not be elevated even in the presence of hypothyroidism. Its serum level may also be influenced by diet.

Other laboratory tests which are helpful in establishing the diagnosis of cretinism are x-rays of the long bones showing late appearance of the centers of ossification and delayed fusion of the epiphyses and/or epiphyseal dysgenesis. A basal metabolic rate determination is of little use in a child, especially an uncooperative one. The serum alkaline phosphatase may be low, and an electrocardiogram may show low voltage throughout with well marked flattening of P and T waves in all leads.

In a cretin in whom the characteristic features are present, diagnosis is not difficult. However, early in the disease when diagnosis is most important the cretin is easily overlooked unless kept in mind. If an infant, such as the case presented, presents symptoms of vomiting and lethargy, intracranial damage may be wrongly diagnosed. Vomiting, constipation and abdominal distension may be confused with intestinal obstruction. Anorexia, vomiting and constipation may be the only complaints of a patient with other diseases, such as cystinosis. These patients are also normal at birth, and as in cretinism, retardation in growth becomes evident during the latter part of the first year or the second year of life. Mongolism, with the protruding tongue, short neck, and other similar features, also needs to be differentiated from cretinism. In mongols the typical features are already

present at birth. Bone age is normal or at least at the lower limit of normal, and psychomotor activity will appear spontaneously without endocrine treatment. Children with cardiac glycogen storage disease may have marked thickening of the tongue and extreme muscular hypotonicity. In this condition there is cardiac enlargement and neurologic abnormalities, and prognosis is very poor. Death usually occurs at 1 to 8 months of age due to cardiac failure or secondary infection.

In other forms of dwarfism, such as gargoylism, chondrodystrophy, rickets, and hypopituitarism, diagnoses can be made by other signs and symptoms and laboratory tests.

The treatment of choice is replacement of the deficient hormone with thyroid extract U.S.P., administered orally once daily beginning with 15 mgm. and increasing by 8 to 15 mgm. every 2 to 3 weeks until a maximal clinical response has occurred or until signs of toxicity appear, at which time the dose should be decreased to the level of the previous dose. Thyroid is a cumulative drug and the maximal effects of a given daily dosage are not attained for 2 weeks. The dosage required varies widely with different patients and has no correlation with body weight or severity of the disease. One writer gives sufficient thyroid to keep his patients just below the toxic level and this requires a dose of 120 to 200 mgm. of the thyroid extract per day irrespective of age. Signs of response include an initial weight loss equivalent to an average of 6 per cent of the body weight during the first 2 to 3 weeks of treatment. The child becomes alert, more active, has better appetite and is not constipated. There is also an improvement in peripheral circulation. The skin becomes warm, the hair glossy. The increase in growth becomes apparent after several weeks. No improvement is seen in the mental status of the patient if mental deterioration has occurred before the therapy was instituted. Nervous disorders such as twitching, speech defect, tremor or spasticity are rarely overcome. Hearing may be improved. Puberty may occur at a normal age.

A guide to the adequacy of treatment would be a complete record of body measurements, developmental status, bone age, serum cholesterol and serum protein-bound iodine.

Thyroid therapy once instituted should be continued indefinitely without interruption except when it is necessary to re-evaluate the need for more thyroid in a child who has been on treatment and who has no physical signs of hypothyroidism or when there is intermittent infection or illness.

Prognosis is favorable as to the physical development if therapy is instituted early but the same can not be said for mental development. Even after many years of therapy few patients achieve the level of dull normal intelligence. This might be due either to an associated cerebral defect or to an irreversible damage produced by hypothyroidism.

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CLINICAL PATHOLOGICAL CONFERENCE

John E. Cassidy, M.D.,* Grace H. Guin, M.D.†

CASE REPORT

This 10½ year old white girl was admitted to the Children's Hospital of the District of Columbia because of chicken pox, and ecchymoses on the right thigh.

Varicella had developed 6 days prior to admission and the course of the disease apparently had been typical, with fever and rash occurring during the first four days of illness. On the third day, four 5 grain tablets of aspirin were administered. On the fifth day an ecchymotic area appeared on the right thigh; this area gradually extended to cover the whole antero-lateral area of the thigh and became very painful. On the day prior to admission another ecchymotic area appeared on the right calf.

The child's past history included measles, mumps and an appendectomy. The parents were living and well. Two siblings had varicella coincident with the patient. One grandfather had diabetes and one uncle had had tuberculosis.

The pertinent physical findings on admission were as follows: The patient was a well developed, well nourished 10½ year old white girl who was in considerable distress, and complained of pain in her right thigh and leg. Her temperature was 99.4 degrees F., pulse rate 86 per minute, and respiratory rate 24 per minute. The typical skin lesions of varicella were profusely distributed over the entire body; many of these lesions had a hemorrhagic base. On the right thigh and right leg were two large bluish-red areas, over which the skin was very tense. The throat was moderately erythematous and there were vesicles on the palate. Decreased breath sounds and dullness to percussion were noted over the right chest.

Laboratory data were as follows: Hemoglobin 12.1 grams per 100 ml., hematocrit

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40 per cent, erythrocytes 3,900,000 per cu. mm., leukocytes 27,000 per cu. mm., with 50 per cent segmented forms, 22 per cent band forms, 12 per cent young forms, 15 per cent lymphocytes, and 1 per cent monocytes. Platelets were below 10,000 per cu mm and many had a bizarre form. Urinalysis: Specific gravity 1.035, albumin 20 mg. per 100 ml., acetone 4 plus, diacetic acid 1 plus; microscopically, there were rare erythorcytes and 2-3 leukocytes per high power field. The bleeding time was four minutes and the Lee-White clotting time was twelve minutes. Clot retraction started after one hour and ten minutes and was complete in twenty-four hours. The prothrombin time was 14 per cent of normal activity. One blood culture showed no growth after two weeks.

Treatment with vitamin K and penicillin was started. The patient took oral fluids well, but complained of pains in the legs and abdomen, and had projectile vomiting during the night of admission. She urinated twice but the amount was not known. On the morning of the following day the patient was cold, clammy, restless, and thirsty. Her blood pressure was 50/0 and her pulse was unobtainable. The heart sounds were distant; the heart rate was 120 per minute. Normal saline and blood were given intravenously; cortisone was also given orally and intravenously. At this time the blood urea nitrogen was 34 mg. per 100 ml. During the day her urinary output was 35 ml. The ecchymotic areas spread to involve the entire right leg and the buttocks. Petechiae appeared over the face. During the evening her blood pressure could not be obtained, and she expired the day after admission, and seven days after the onset of varicella.

DISCUSSION

Dr. Cassidy:

In summary we have a 10½ year old girl with varicella of six days duration who obviously has a coagulation defect of some sort, who prior to the onset of this coagulation defect had received 20 grains of aspirin, and who also has some abnormal physical signs in the right chest.

First of all we should consider the possible complications of varicella. Serious complications are extremely rare, and in the order of frequency include pneumonia, secondary infection of the primary lesions, and encephalitis. An acute glomerulonephritis may follow secondary infection of the skin lesions. In patients with varicella without secondary infection of primary lesions acute glomerulonephritis is practically unheard of. Certainly this patient did not have secondary infection of her lesions, or evidence of encephalitis, but she did have possible pulmonary involvement.

The next point to be considered in this case is the cause of the hemorrhagic diathesis. Coagulation defects, for purposes of discussion may be divided into three main groups: those associated with abnormality of the platelets, those associated with disturbance of the plasma proteins active in coagulation, and those associated with damage to the vessel walls. In the first group, of course, are the purpuras, the thrombocytopenic and the non-thrombocytopenic. Thrombocytopenia may be primary (idiopathic) or secondary to a blood dyscrasia such as leukemia, overactivity of the spleen and reticuloendothelial system, or infection. In the nonthrombocy-

topenic group are the so-called allergic purpuras, those secondary to various chemical agents, and those associated with abnormal functioning of the platelets, the thrombasthenias.

Those coagulation defects associated with disturbances of proteins present in the plasma include classical hemophilia and the hemophilia-like diseases, and hypoprothrombinemia. Hypoprothrombinemia can be subdivided into acquired and congenital types. The congenital form may be disregarded in this particular instance. The acquired hypoprothrombinemias may be due to a dietary vitamin K deficiency or to medication with antibiotics which disturb the intestinal flora and interfere with the synthesis of vitamin K in the intestine, or to poor absorption because of disturbance of the flow of bile into the small intestine. In the presence of liver disease, there may be actual interference with synthesis of prothrombin. Certain drugs such as aspirin and Dicumarol® can interfere with synthesis of prothrombin in the liver by interfering with the action of vitamin K. The so-called hypoprothrombinemia of the newborn is not a single deficiency, but is associated very frequently with diminution of both plasma thromboplastin and plasma proconvertin. It is seldom a pure prothrombin deficiency.

In the group of bleeding disorders due to disturbances of the vessel wall, we think of scurvy; we also think of the thrombasthenias in which the

FIG. 1. Massive ecchymoses and petechiae

constrictor substance present in the platelets is not set free to cause the constriction of the smaller vessels.

Now let us consider the laboratory data in this child. She had a thrombocytopenia and a marked diminution in prothrombin level. There was also a marked leukocytosis with a definite left shift, which could be explained either on the basis of hemorrhage, secondary infection associated with the chicken pox, or merely extensive chicken pox alone.

The coagulation studies which are reported do not quite substantiate the laboratory finding of thrombocytopenia. When a thrombocytopenia is present there is usually a prolongation of bleeding time and clot retraction time, and a normal coagulation time. In this case these tests were all within normal limits. We would like to have seen the result of an examination of the bone marrow, but since this test was not performed we must simply state that the coagulation defect is probably due to thrombocytopenia and hypoprothrombinemia.

If this patient's hypoprothrombinemia were on the basis of liver damage the administration of vitamin K would be useless due to interference with the actual synthesis of prothrombin. In such instances the administration of fresh blood is the only thing capable of correcting the condition. The patient went into profound shock, became oliguric and died. The patient with

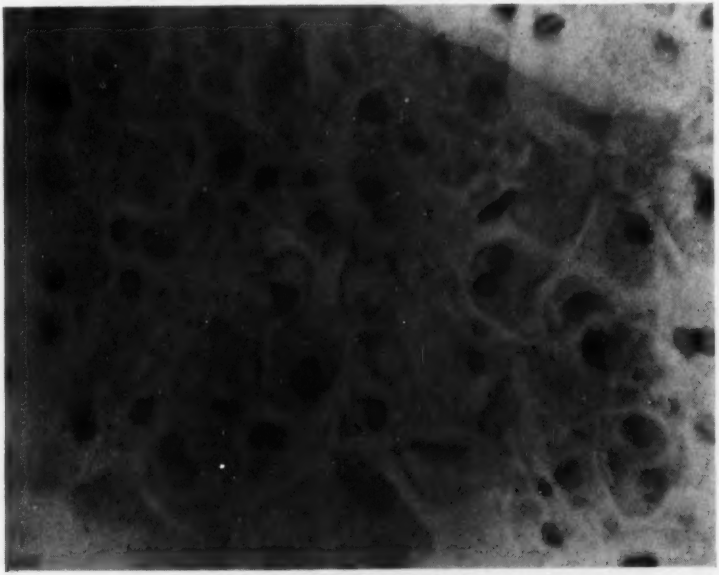

FIG. 2. Hepatic degeneration

a coagulation defect who does this almost certainly has a fairly massive hemorrhage as the terminal event. There is not enough information to help us localize such hemorrhage although there was pain in the abdomen, so it is possible that the patient had some intraperitoneal hemorrhage. She may have had some hemorrhage in the left pleural space, as suggested by the abnormal chest signs which were present on admission, and there may even have been some intracranial hemorrhage. The oliguria which developed could possibly have been due to the profound shock with decrease of blood flow through the kidneys, and the production of the so-called lower nephron nephrosis syndrome. This syndrome may also occur when there is considerable hemorrhage in the tissues.

We still have nothing that could account for the thrombocytopenia. We have to keep in mind the primary blood disturbances, such as leukemia, although we cannot confirm or rule these out. There may also have been pre-existing liver damage, possibly as a result of the varicella which made this patient more susceptible to aspirin or other toxic agents to which she may have been sensitive.

I think as a final diagnosis we would have to say the patient had chicken pox accompanied by a coagulation defect which could conceivably have been due to an idiosyncrasy to aspirin. This coagulation defect was probably due also to the thrombocytopenia, the cause of which we do not know. The

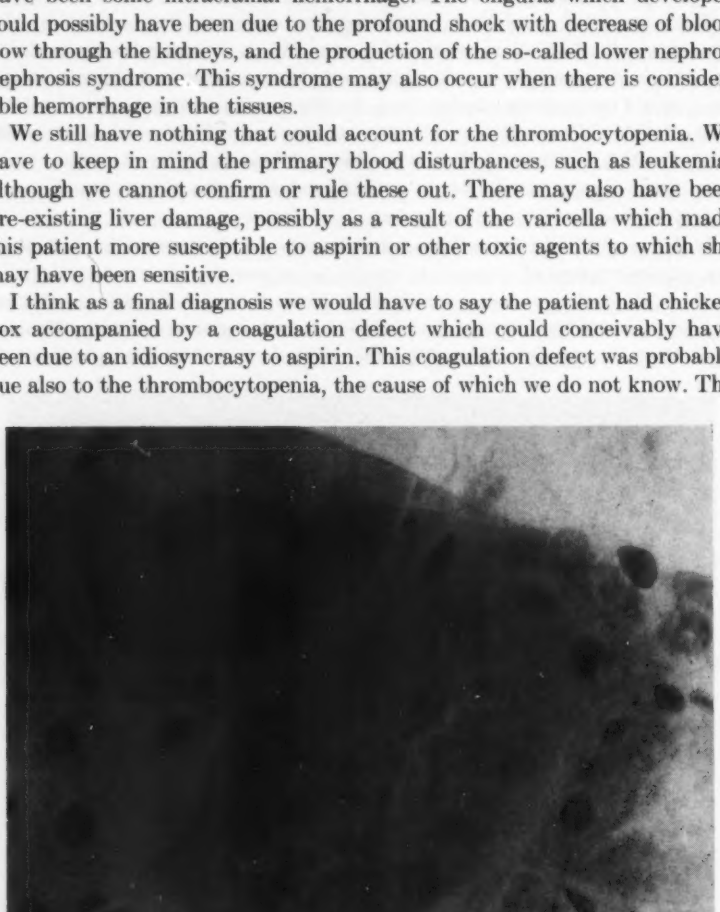

FIG. 3. Kidney showing degeneration of proximal convoluted tubules

patient did have a terminal massive hemorrhage with shock and renal damage.

Dr. Guin:

The histologic picture of varicella reveals a herpetic lesion in which there is a splitting of the epidermis with vacuolization and influx of plasma. After a few days the lesion is no longer clean, but has a purulent aspect as a result of inflammatory cell infiltration. A histologic diagnosis of chicken pox can be made if certain criteria are present. The so-called balloon cell is noted in the basal layer of epithelium. The ballooning is merely the reflection of degeneration and the presence of intracellular fluid. In the nuclei of these cells, there are masses of eosinophilic material, the Lipschutz bodies, which are characteristic of varicella. The lesions of varicella are not necessarily confined to the skin; they can extend into the buccal cavity and into the trachea.

Figure 1 illustrates the hemorrhagic lesions which appeared on the child's legs. There was a considerable amount of focal necrosis of the liver (Fig. 2); clinically, there was a depression of blood prothrombin. The glomeruli of the kidneys were not remarkable. Figure 3 illustrates the cellular degeneration of two of the proximal convoluted tubules. Both kidneys showed similar changes. This is the picture of necrosis of proximal convoluted tubules rather than a lower nephron nephrosis. Apparently, some "toxin" from the varicella was responsible for these irreversible changes in the kidneys.

The lungs showed only a moderate degree of vascular congestion. This patient did not exhibit any lesions in the mucosa of her respiratory tract. The brain showed some edema but no hemorrhage. The adrenal glands were not remarkable. Post-mortem bone marrow examination revealed depression of the hematopoietic elements which would be consistent with a secondary reaction to a toxin rather than to hypersplenism.

We attribute the death of this child to the overwhelming toxicity of the varicella virus. Several pediatricians commented that in the year of this child's death (1952), varicella seemed to be particularly severe. About three years ago we saw the slides from an autopsy of a baby that was born to a mother with varicella. Chicken pox developed and the child died. The lesions in that case extended down into the respiratory mucosa, and there was an extensive pneumonia, but no hemorrhagic stigmata.

Dr. Cassidy:

Your diagnosis certainly is correct, but I think we have to consider in addition the possibility of the aspirin acting as a toxic agent.

Dr. Guin:

We cannot rule that out. We think that whatever this toxin was, it was the cause of the depression of the bone marrow as well as of the focal necrosis of the liver and kidney tubules.

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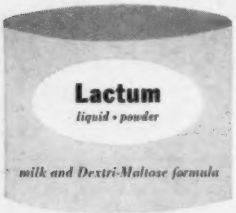

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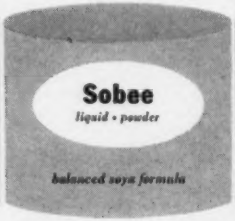

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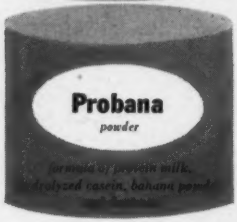

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